

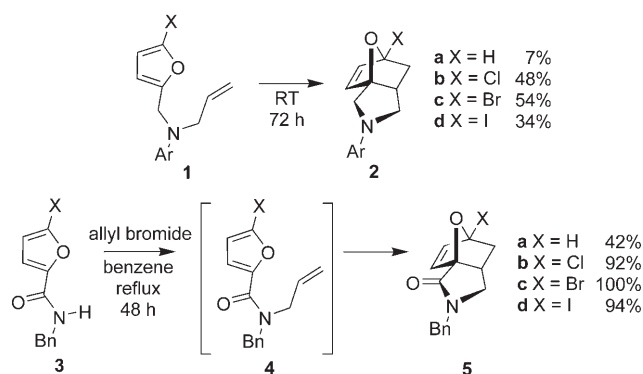
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# The Origin of the Halogen Effect on Reactivity and Reversibility of Diels–Alder Cycloadditions Involving Furan\*\*

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Diels–Alder reactions involving furan as a diene are valuable processes, yielding versatile oxanorbornenes that have been used in the syntheses of numerous complex molecular architectures<sup>[1]</sup> such as prostaglandins<sup>[2]</sup> and terpenoids.<sup>[3]</sup> Furan substitution greatly affects the viability of these reactions. Halogen substituents have been found to increase rates and yields. In addition, halogen atoms can be easily removed<sup>[4]</sup> or used as handles in carbon–carbon bond-forming reactions.<sup>[5]</sup> Klepo and Jakopcic found that chlorine, bromine, or iodine substituents on furan increase cycloaddition yields and cycloadduct stability (see yields for conversion of **1** to **2**).<sup>[6]</sup> More recently, Padwa and co-workers found that conversions of furanylamides **3b–d** to **5b–d** proceed at higher rates and increased yields than the unsubstituted system **3a** to **5a** (Scheme 1).<sup>[7]</sup>

The possibility that simple halogen substitution might convert previously failed furan cycloadditions into successes



**Scheme 1.** Intramolecular reactions. Bn = benzyl.

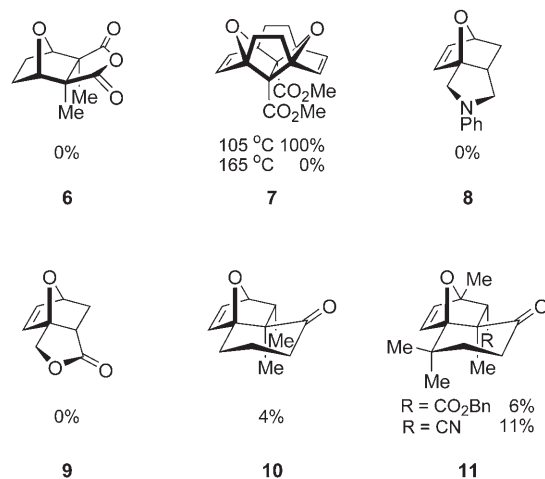
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caused us to explore the origin and generality of this halogen effect. A number of apparently reasonable cycloadditions have been found to be unsuccessful, usually due to substrate inertness<sup>[8]</sup> or the tendency for products to undergo retrocycloadditions.<sup>[9–11]</sup> A celebrated example is the unattainable direct synthesis of cantharidin (**6**).<sup>[12]</sup> Figure 1 illustrates



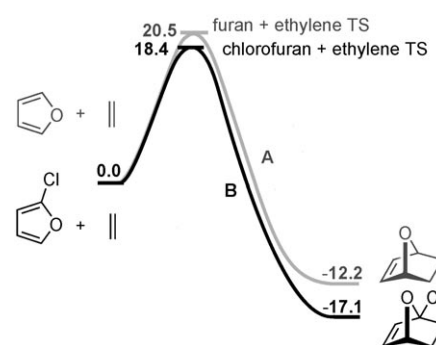
**Figure 1.** Furan-Diels-Alder adducts formed in low or negligible yields (**6–11**).

products of failed cycloadditions (**8** and **9**) as well as low-yielding cycloadditions (**10** and **11**).<sup>[11,13]</sup> Cram's polycycle (**7**) exemplifies the sensitivity of these reactions to retrocycloadditions at increased temperatures.<sup>[14]</sup> This reversibility has been used to advantage for self-healing polymers prepared by Wudl et al.<sup>[15]</sup>

The halogen effect and the possibility that it might facilitate these unsuccessful cycloadditions were explored with high-accuracy CBS-QB3<sup>[16]</sup> computations.<sup>[17]</sup> The much faster B3LYP/6-31G(d) calculations of energetics are accurate for many hydrocarbon pericyclic reactions,<sup>[18]</sup> but we have found systematic errors for hetero systems<sup>[19]</sup> and had to resort to the more CPU-intensive calculations. The nature of stationary points was confirmed by frequency analysis.

Diels-Alder cycloadditions of furan and 2-chlorofuran with ethylene are predicted to have activation enthalpies of 20.5 and 18.4 kcal mol<sup>−1</sup>, respectively (Figure 2). The corresponding reaction enthalpies are −12.2 and −17.1 kcal mol<sup>−1</sup>. The larger stabilization of the product by the chlorine substituent, as compared to reactants and transition state, produces a change in activation enthalpy (2.1 kcal mol<sup>−1</sup>) that is about one-half the change in reaction energy (4.9 kcal mol<sup>−1</sup>). This increase in exothermicity upon substitution is accompanied by a smaller decrease in activation barriers, indicating that the stabilizing effect of halogens increases with bond formation between diene and dienophile.

The kinetic and thermodynamic facilitation of furan cycloadditions are general with halogen substitution on the diene (Table 1). Halogen substitution increases reaction exothermicities by 4–9 kcal mol<sup>−1</sup>, and decreases activation barriers by 2–3 kcal mol<sup>−1</sup>. Reactions involving 2-fluorofuran are predicted to have the greatest increases in exothermicity,



**Figure 2.** The Diels-Alder reaction of 2-chlorofuran and ethylene (curve B) has a lower activation enthalpy and is more exothermic than the reaction of furan (curve A). Enthalpies are given in [kcal mol<sup>−1</sup>].

**Table 1:** CBS-QB3-calculated activation and reaction enthalpies [kcal mol<sup>−1</sup>] for the reactions of furan and halogenated furans with ethylene.

| Reaction | $\Delta H^\ddagger$ | $\Delta H_r$ |
|----------|---------------------|--------------|
| 1a       | 20.5                | −12.2        |
| 1b       | 18.3                | −17.3        |
| 1c       | 18.4                | −17.1        |
| 1d       | 17.1                | −20.9        |
| 2b       | 18.0                | −16.0        |
| 2c       | 18.1                | −16.0        |
| 2d       | 18.6                | −16.2        |

while bromine and chlorine should affect exothermicities to the same extent. This trend is also found for the cycloaddition energy barriers. Halogenation has a greater effect on the exothermicities at the 2- rather than at the 3-position of furan. Since  $-T\Delta S$  is approximately +12 kcal mol<sup>−1</sup> at 25 °C for each of these reactions, the halogen causes a reversible reaction ( $\Delta G \approx 0$ ) to become significantly exergonic.

Several other representative substituents were investigated for comparison (Table 2). Methyl substitution lowers activation enthalpies by less than 1 kcal mol<sup>−1</sup> and increases exothermicities by less than 2 kcal mol<sup>−1</sup>. These energy

**Table 2:** Calculated activation and reaction enthalpies [kcal mol<sup>−1</sup>] for the reactions of methyl-, trifluoromethyl-, and methoxyfuran with ethylene.

| Reaction | $\Delta H^\ddagger$ | $\Delta H_r$ |
|----------|---------------------|--------------|
| 1a       | 20.5                | −12.2        |
| 3b       | 19.9                | −13.2        |
| 3c       | 18.1                | −16.9        |
| 3d       | 18.8                | −17.9        |
| 4b       | 19.5                | −14.0        |
| 4c       | 19.4                | −14.1        |
| 4d       | 18.3                | −18.3        |

changes are significantly smaller than those caused by halogen substitution and reflect the general energetic preference for branching hydrocarbons. The trifluoromethyl group, which is comparable in electronegativity to chlorine and bromine, lowers activation enthalpies by 1–2 kcal mol<sup>-1</sup> and increases exothermicities by 2–5 kcal mol<sup>-1</sup>. As observed for halogens, the greatest changes in energetics occur in reactions involving 2-substituted furans. The methoxy group is a commonly used substituent in furan cycloadditions,<sup>[1b]</sup> and is predicted to lower activation enthalpies by 2 kcal mol<sup>-1</sup> and increase exothermicities by 6 kcal mol<sup>-1</sup>.

To determine if the halogen effect is unique for furans, hydrocarbon diene cycloadditions were explored (Table 3).

**Table 3:** Activation and reaction enthalpies [kcal mol<sup>-1</sup>] for the Diels–Alder reactions involving hydrocarbon and halogenated dienes.

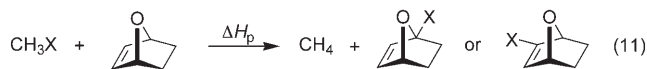
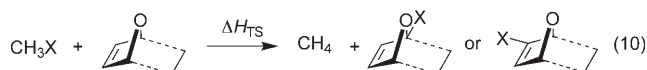
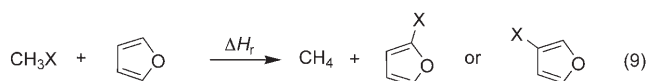
a X = H  
b X = Br  
c X = Cl  
d X = F

(5)–(8)

| Reaction | $\Delta H^\ddagger$ | $\Delta H_r$ |
|----------|---------------------|--------------|
| 5a       | 21.5                | -40.3        |
| 5b       | 19.8                | -44.2        |
| 5c       | 20.0                | -42.5        |
| 5d       | 20.6                | -43.3        |
| 6a       | 16.1                | -26.4        |
| 6b       | 14.6                | -29.9        |
| 6c       | 14.9                | -29.4        |
| 6d       | 14.6                | -31.3        |
| 7b       | 20.0                | -42.6        |
| 7c       | 20.5                | -42.4        |
| 7d       | 22.0                | -41.6        |
| 8b       | 14.5                | -28.3        |
| 8c       | 14.8                | -28.0        |
| 8d       | 16.1                | -26.8        |

The same kinetic and thermodynamic effects found for furan are also observed in the hydrocarbon dienes. Activation barriers are decreased by 0–2 kcal mol<sup>-1</sup> and reaction exothermicities are increased by 0–4 kcal mol<sup>-1</sup>. Halogen substitution has a smaller effect on hydrocarbon dienes than on furan. Reaction enthalpies are significantly larger for reactions involving unsubstituted hydrocarbon dienes than for furan ( $\Delta\Delta H = 14$ –28 kcal mol<sup>-1</sup>). As a result, halogen substitution greatly impacts furan cycloaddition energetics, in contrast with their hydrocarbon counterparts.

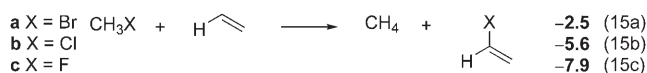
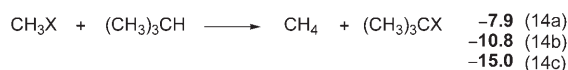
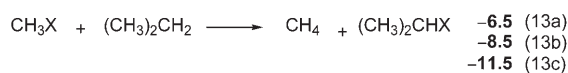
Isodesmic Equations (9)–(11) were examined to determine the effect of halogenation on diene, transition state, and product, separately. The increased exothermicities in the reactions involving halogenated furans (Table 1) correspond with a larger stabilization of the adducts (3.6–14.0 kcal mol<sup>-1</sup>) over the reactants (–0.2–5.3 kcal mol<sup>-1</sup>; Table 4). The stabilizations are approximately in the order of electronegativities, although chlorine and fluorine are sometimes reversed. This stabilization is parallel for bromine and chlorine substituents along the reaction coordinate, resulting in identical overall effects on reaction enthalpies (Table 1).



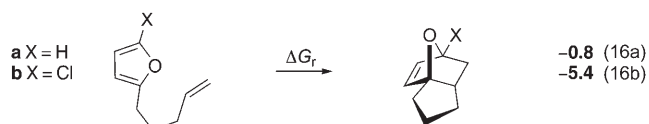
**Table 4:** Decomposition of reactant, transition state, and product stabilization [kcal mol<sup>-1</sup>] using isodesmic Equations (9)–(11).

|        | Diene           | $\Delta H_r$ | $\Delta H_{TS}$ | Product           | $\Delta H_p$ |
|--------|-----------------|--------------|-----------------|-------------------|--------------|
| X = H  | furan           | 0.0          | 0.0             | X-furan           | 0.0          |
| X = Br | furan           | 0.2          | -1.9            | X-furan           | -4.8         |
| X = Cl | furan           | -3.5         | -5.7            | X-furan           | -8.5         |
| X = F  | furan           | -5.3         | -8.8            | X-furan           | -14.0        |
| X = H  | cyclopentadiene | 0.0          | 0.0             | X-cyclopentadiene | 0.0          |
| X = Br | cyclopentadiene | 0.2          | -2.3            | X-cyclopentadiene | -3.6         |
| X = Cl | cyclopentadiene | -2.9         | -5.4            | X-cyclopentadiene | -6.7         |
| X = F  | cyclopentadiene | -1.9         | -3.7            | X-cyclopentadiene | -5.9         |

Comparison of isodesmic Equations (12a)–(12c) with (15a)–(15c) suggests a small effect due to change of hybridization from sp<sup>2</sup> to sp<sup>3</sup>. Stabilization of these systems by electronegative substituents has been ascribed to a combination of n → π\* resonance in unsaturated systems, hyperconjugation, and orbital electronegativity effects.<sup>[20]</sup> The larger effect is the energetic preference for electronegative halogens to be attached to a more highly alkylated, and therefore more electropositive, carbon framework as provided in the Diels–Alder product. The series of isodesmic reactions in Equations (12)–(14) illustrates the generality of this preference. Exothermicity increases substantially with each additional methyl group on the carbon bearing the electronegative substituent (tertiary > secondary > primary), a general effect widely observed.<sup>[21]</sup> These observations have been explained by Schleyer using an analogy with carbocations.<sup>[20]</sup> Electropositive groups stabilize both carbocations and carbon centers carrying electronegative substituents by means of hyperconjugative and σ-inductive effects.



The results show that halogenation of dienes is beneficial in Diels–Alder reactions, both increasing the rates and yields of these reactions. Intramolecular Diels–Alder reactions involving furan have a tendency for retrocycloaddition,<sup>[10]</sup> but halogenation makes the reaction more exergonic. For example, an unsubstituted analog of systems **1** and **3** [Eq. (16a)] is predicted to have  $\Delta G_r = -0.8 \text{ kcal mol}^{-1}$ , essentially zero within expected error. Halogen substitution would cause this reaction [Eq. (16b)] to become more clearly exergonic ( $\Delta G_r = -5.4 \text{ kcal mol}^{-1}$ ). The large effects of halogen substitution in experimental cases **1b–d** and **3b–d**, are in good agreement with calculations.



Alkyl substitution has a small and similar effect on both activation and reaction energies, while electronegative groups are much more influential. The trifluoromethyl group exhibits comparable effects to halogens at the 2-position of furan. Alkoxy groups and halogens are not only beneficial to the energetics of these reactions, but provide functionalities for further transformations. A detailed analysis of other substituent effects involving attachment of two electronegative atoms to one carbon atom (e.g. anomeric effect), and the study of synthetically useful intramolecular Diels–Alder reactions involving halogenated furans are in progress.

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